https://doi.org/10.32921/2225-9929-2024-1-56-59-65
UDC 616-089.843
IRSTI 76.29.46

Review article

Solid Organ Transplantation in Kazakhstan: A Review on Current Situation and Challenges

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Abstract

Transplantation is one of the important strategic directions of medicine in Kazakhstan, which has been intensively developing in recent years. Noteworthy progress is observed in the implementation of advanced transplantation technologies aligned with global standards within scientific institutions and regional clinics across the country. However, there are certain problems in this field associated with the shortage of organs, transplantation for individuals in advanced disease stages, the growing need for re-transplantation, and adverse effects associated with immunosuppressive therapy. In this review, we aim to summarize the current situation of solid organ transplantation in Kazakhstan and the challenges hindering transplantation in the country.

A literature search encompassing the Cochrane Library, Medline, and EMBASE, spanning until December 2023, was conducted. Search was done manually and using the following keywords: transplantation in Kazakhstan, liver transplantation, kidney transplantation, heart transplantation, coordination centers, and immunosuppression.

For the effective work of the transplant coordination service and the provision of donors to the population, an integrated approach is needed, including organization of educational campaigns to disseminate information among the population, expanding the network of transplant coordination centers, creating a donation model based on the presumption of consent, and eliminating the free disposal of human organs.

Keywords: *liver transplantation, heart transplantation, kidney transplantation, organ donation, Kazakhstan*

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J Health Dev 2024; 1 (56): 59-65
Recieved: 09-02-2024
Accepted: 05-03-2024

Introduction

Over the past five decades, transplantation has undergone global success as a medical procedure. Advancements in surgical techniques, the progress of immunosuppressive medications, and the refinement of methods for handling biological materials have collectively contributed to the development of the transplantation of vital organs offering viable solutions for individuals with severe chronic diseases [1-2].

Transplantation stands as a crucial and actively advancing field of medicine in Kazakhstan, with notable progress in recent years. Advanced transplantation technologies conforming to global standards are effectively implemented in research hospitals and regional clinics across the country. Nonetheless, challenges persist in this sector, including the shortage of donor organs, transplantation for patients in advanced disease stages – the rapid progression of the disease to advanced stages while the recipient is waiting for a suitable donor ?, an increasing demand for re-transplantation, and concerns related to the toxicity and side effects of immunosuppressive therapy.

In Kazakhstan's history, a milestone in transplantology was marked in 1979 when the Institute of Experimental and Clinical Surgery successfully conducted the first kidney transplant operation from a deceased donor.

Historically the milestone in Kazakhstani transplantology was marked in 1979, with the first deceased donor kidney being successfully transplanted at the Institute of Experimental and Clinical Surgery in Almaty.

Taking the Spanish model of organ donation and transplantation as a key reference, Kazakhstan has established a national organ donation system, structured around transplant coordination centers employing a three-tier management model. The entire procedure of organ transplantation in Kazakhstan is covered by the state budget, i.e. guaranteed volume of free medical care, and hence is free for the patients [3].

Solid organ transplantation has proven itself to be the optimal therapeutic choice for individuals facing terminal diseases, offering a life-saving or life-prolonging solutions [4].

The current quantity of solid organ transplantations performed in Kazakhstan and comparison with Global and Europe indicators is shown in Table 1.

Table 1 - Quantity of solid organ transplantations in Kazakhstan in comparison with global indicators for 2022

Data presented in absolute number and rate per million people (pmp)	Kazakhstan	Europe	Global
Actual deceased donors (DD)	4 (0.21)	11,657 (16.85)	40,977 (6.87)
Actual DD after circulatory death (DCD)	(-)	2,483(3.59)	9,282 (1.56)
Total kidney transplantations	176 (9.17)	25,361 (36.66)	102,122 (17.12)
Deceased kidney transplantations	7 (0.36)	17,302 (25.01)	62,505 (10.48)
Living kidney transplantations	169 (8.8)	8,059 (11.65)	39,617 (6.64)
Total liver transplantations	43 (2.24)	9,840 (14.22)	37,436 (6.28)
Deceased liver transplantations	2 (0.1)	8,055 (11.64)	28,343 (4.75)
Living liver transplantations	41 (2.14)	1,773 (2.56)	9,060 (1.52)
Heart transplantations	4 (0.21)	2,444 (3.53)	8,988 (1.51)
Lung transplantations	3 (0.16)	2,073 (3)	6,784 (1.14)
Pancreas transplantations	(-)	611 (0.88)	2,026 (0.34)
Small intestine transplantations	(-)	40 (0.06)	170 (0.03)
Total organ transplantations	226 (11.77)	40,369 (58.35)	157,526 (26.41)

Population in Kazakhstan: 19.20 million inhabitants.
Source: GLOBAL OBSERVATORY ON DONATION AND TRANSPLANTATION
https://www.transplant-observatory.org/summary/

This table demonstrates that kidney transplantations are done more often compared to other solid organs worldwide and in Kazakhstan. Pancreas transplantation and small intestine transplantation are not performed in Kazakhstan yet.

In this review, we aim to summarize the current situation of solid organ transplantation in Kazakhstan and the challenges that hinder further development of the program in the country.

Methodology

A literature search was conducted on PubMed, ResearchGate, Cyberleninka, eLibrary, Medline, and EMBASE until December 2023. All searches for literature reviews were performed manually and using the following keywords: transplantation in Kazakhstan, liver transplantation, kidney transplantation, heart transplantation, coordination centers, and immunosuppression. The review included primary studies (descriptive and analytical studies), secondary studies (systematic reviews and meta-analyses), methodological manuals, clinical manuals, as well as full-text publications in Russian and English over the past 10 years.

Ethics approval. This study was conducted in strict accordance with the principles outlined in the Helsinki Declaration. Prior to the commencement, approval from the University Medical Center local ethics committee was obtained.

Liver transplantation in Kazakhstan

Liver transplantation is recognized as a proven and definitive treatment for various causes that result in end-stage liver disease (ESLD), including cirrhosis, nonalcoholic steatohepatitis, hepatocellular carcinoma, and metabolic diseases. For the first time, orthotopic liver transplantation (OTP) was performed by an American surgeon T. Starzl in 1963. Nevertheless, owing to the intricate nature of liver transplantation surgery, the initial procedure and several subsequent transplantations faced serious complications, leading to patient deaths either during or shortly after the surgery [5].

The first heterotopic liver transplant in Kazakhstan was performed in 1996. A living-donor liver transplantation is an independent direction in transplantation. For the first time in Kazakhstan such surgery was performed in 2011 at the National Research Center of Surgery with the participation of surgeons from Belarus. 2013 marked the first in Kazakhstan orthotopic liver transplantation from a deceased donor [6].

Vast majority of people in Kazakhstan who are in the waiting list for liver transplantation have liver cirrhosis, with viral and autoimmune causes being prevalent. In cases of viral hepatitis, transplant doctors usually rely on living-donor liver transplantation, whereas deceased donor livers are typically involved in situation when liver transplant is required due to various autoimmune liver diseases. The choice of living donors for viral end-stage liver diseases may be influenced by the potential application of antiviral therapy at various disease stages, in contrast to the lack of control over autoimmune liver diseases, necessitating urgent procedures with deceased donors. Recipients of livers from living donors need a longer recovery period due to the requirement to attain the initial liver volume [7].

Due to the ethical and legislative aspects, transplants from deceased donors are performed much less frequently. In Kazakhstan, these surgeries are civered by state budget (so-called guaranteed volume of free medical care), as well as in the postoperative period, all patients are provided with the necessary immunosuppressive therapy.

For immunosuppressive therapy next medicines are prescribed: basiliximab (20 mg), prednisolone (500-1000 mg), tacrolimus (1.0 mg/day), mycophenolate (1000 mg/day) within the guaranteed volume of free medical care [8].

Kazakhstan, has recently committed to health system transformation, which will include enactment of presumed consent legislation in 2020 (Code of the Republic of Kazakhstan "On the health of the people and the healthcare system). However, practice shows that specialists are faced with the almost insurmountable problem of refusal of relatives of the deceased to give consent to organ transplantation. The reasons for refusal are the following factors: moral, religious barriers, lack of awareness of the population about the possibilities of reducing mortality and improving the quality of life of people in need of organ and tissue transplants, misinterpretation of the norms of the current legislation on transplantology, fear of the risk of commercialization and criminalization [9].

Kidney transplantation in Kazakhstan

Kidney transplantation stands as the most optimal treatment choice for individuals dealing with end-stage renal disease (ESRD). Among various renal replacement methods, kidney transplantation (KTx) emerges as the most effective therapeutic choice. KTx not only significantly improves patient survival but also surpasses other renal replacement therapies in enhancing overall quality of life. The first kidney transplantation in Kazakhstan was done in 1979, and it took over two decades to develop a thoroughly organized transplantation program. The prevalence of ESRD is rapidly rising in Asia, where the affected patient population tends to be notably young (40-50 years old), in contrast to Western countries [10].

In other studies, the most prevalent complications observed among kidney recipients included infections, rejection, and surgical issues. It has been established that instances of acute rejection elevate the likelihood of graft loss in kidney recipients.

Desensitization protocols are not widely used in Kazakhstan. Recipients were prescribed a heightened immunosuppression regimen before KTx, and in all cases, the cross-match test yielded negative results [11].

Since 2010, the number of kidney transplantation cases in Kazakhstan is continuously increasing: over 200 cases are being performed annually. Kidney transplantation from living donor who is usually a family member is the most common in Kazakhstan. A very few cadaveric transplantations are performed in Kazakhstan; the high prevalence of living donor kidney transplantation is common for Asian countries, 83-90 % of kidneys come from living donors [12].

As per the findings of the Global Burden of Disease study, Kazakhstan reported 1.78 million individuals with chronic kidney disease in 2017, resulting in 1485 deaths -approximately 1% of the total mortality reported that year. Presently, there are 2963 individuals on the kidney waiting list in Kazakhstan.

Like many Asian countries, kidney transplantation (KTx) from living donors is predominant in Kazakhstan. The shortage of organs persists due to the negative attitudes towards organ donation [13].

Kidney transplantation proves to be a financially advantageous choice for individuals with chronic kidney disease (CKD). In Kazakhstan, the expense for hemodialysis per patient amounted to 10,000 USD annually, whereas the cost of kidney transplantation was 7.500 USD in 2019 [14].

Heart transplantation in Kazakhstan

Christiaan Barnard conducted the first human-to-human heart transplantation in Cape Town on December 3, 1967. Heart transplantation stands as the preferred treatment for individuals facing end-stage heart disease and heart failure. Nevertheless, mortality rates in heart transplantation are notably high, primarily due to the donor organ failure [15].

The shortage of donor hearts confines this treatment to a small proportion of potential recipients. Allocating the limited donor hearts necessitates consideration from two distinct viewpoints. First, the assessment involves weighing the risks and benefits for the individual patient. Second, the evaluation extends to the patient's ability to derive benefits compared to the broader group of potential recipients [16].

In 2011, Kazakhstan initiated its national heart failure program, and in 2012, the heart transplantation program was launched. Additionally, Left Ventricular Assist Devices (LVAD) program was established in 2011 to offer mechanical circulatory support to individuals facing end-stage heart failure. This was done at the National Research Center for Cardiac Surgery (NRCCS) in Astana, Kazakhstan. The existence of the Ventricular Assist Devices (VAD) program is currently facilitating the growth of heart transplantation in Kazakhstan.

Given the traditional methods of preserving donor organs, prolonged cold ischemic time stands out as a critical risk factor for primary allograft dysfunction, morbidity, and mortality in heart recipients. To tackle this challenge, two ex vivo preservation methods are employed: cold storage and a system for ex vivo heart perfusion. Considering the long distances from various regions to NRCCS in Astana (exceeding 1000 km), preserving donor organs during transportation becomes a challenge [17].

With an increasing number of patients now being in need for transplantation, a significant imbalance between supply and demand exists.

Discussion

The issue of organ transplantation is present not only in Kazakhstan but worldwide, as a severe shortage of donor organs contributes to high mortality rates among patients requiring organ and tissue transplantation. To address the organ shortage, various measures are widely employed, including organ transplantation from deceased and living donors, multi-organ retrieval, and the development of new methods for organ preservation and transportation. Xenotransplantation might be a promising alternative approach to bridge the gap between the supply and demand of organs, tissues, and cells; however, immunological barriers are limiting factors in clinical xenotransplantation. Thanks to advances in gene-editing tools and immunosuppressive therapy as well as the prolonged xenograft survival time in pig-to-non-human primate models, clinical xenotransplantation has become more viable [18].

Currently, there is an upsurge in the number and quality of transplants, and progress is evident globally. Spain, Belgium, Austria, and Portugal have achieved significant success in this field, particularly in increasing the number of donations and enhancing the training of transplantation specialists and coordinators.

The primary obstacle hindering the progress of transplantation worldwide is the shortage of donor organs. The economic viability of transplantation as a treatment method, demonstrated through the reduction of direct and indirect treatment costs for patients and the enhancement of the quality of life among the working population, has been established.

The disparity between demand and supply is particularly evident among low-income and middle-income countries globally, with significant variations in access to suitable transplantation and variations in the levels of safety, quality, and efficacy in the donation and transplantation of human cells, tissues, and organs.

Since the first heart transplant in Kazakhstan in 2012, 12 years have passed. During this time, the solid organ transplantation in Kazakhstan has achieved notable success. Liver, kidney, heart, lung transplantation are now routinely performed in the country.

The number of transplanted patients is increasing in the country, with an average of 200 patients undergoing organ transplantation per year. The quality of surgeries and postoperative care is aiming towards the international standards. The one-year survival rate for kidney recipients is 95-97%, for liver recipients it is 85%, and for heart recipients, it is 86% [19].

The Republican Center for Transplant Coordination and High-tech Medical Services (referred to as the Coordination Center) was established in 2018, modeled in accordance with the Spanish system. According to the data from the Coordination Center, as of 2023, there are 3,916 patients on the waiting list in need of organ transplantation, including 110 children. Among those, the vast majority of the patients require a kidney transplant, which is 3,565 people (91.2%), followed by 185 patients (4.5%) in need of a liver transplant, 146 (3.7%) - heart transplant, 15 (0.4%) – lung transplant, and 5 (0.1%) are in need of pulmonary-cardiac complex . Currently, there are 8 transplant centers in the country, staffed by highly qualified specialists and equipped according to current standards.

From 2012 to October 2023, 2573 transplant surgeries were conducted, with 424 (17.9%) from deceased donors. Due to a low number of donors and a significant number of refusals for deceased organ donation, the number of organ transplants in Kazakhstan from living donors is much higher than those from deceased donors, accounting for 82.1% and 17.9%, respectively. On the contrary, in countries such as the USA, Spain, Croatia, and Iran, at least 85% of transplantations are from deceased donors.

In Kazakhstan, there are 40 donor organizations with specialized departments (intensive care, stroke center, polytrauma) providing medical services to prepare cadavers for multi-organ transplantation (organ parts) and/or tissue (tissue parts) transplantation.

The organ transplant system in Kazakhstan faces several significant challenges:

-Shortage of donor organs, particularly from deceased donors;

-Substantial distances between hospitals donating deceased-donor organs and transplant centers;

-Lack of availability of HLA-testing laboratories;

-Shortage of skilled transplant teams;

-Absence of alternative immunosuppressive medications like sirolimus, everolimus, and others that are not registered in Kazakhstan;

-Limited access to appropriate postoperative patient care due to a scarcity of experienced nephrologists in the regions of Kazakhstan [20];

-For effective functioning of the transplant coordination service and timely provision of donor organs to the population, an integrated approach is necessary, including:

-Organization of educational campaigns to raise awareness about critical need for donors and shift public opinion in favor of organ donation;

-Expanding the network of transplant coordination centers and organizing continuous training to develop highly qualified specialists in this field.

-Developing a donation model based on the presumption of consent, excluding the free disposal of human organs.

Conclusions

For the effective work of the transplant coordination service and the provision of donors to the population, an integrated approach is needed, including organization of educational campaigns to disseminate information among the population, expanding the network of transplant coordination centers, creating a donation model based on the presumption of consent, and eliminating the free disposal of human organs.

Conflict of interest. The authors declare no conflict of interest

Funding Information. This research is funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan (Grant title: Non-invasive methods for diagnosis of transplant rejection as a predictor of long-term graft survival, Grant No. BR21882206).

Authors' contributions. Conceptualization – Yuryi Pya; methodology – Asanova Aruzhan; verification - Shaysultanova Saule; formal analysis – Altynova Sholpan; writing (original draft) – Gulnur Daniyarova; writing (review & editing) – Abdiorazova Aigerim

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Қазақстандағы паренхиматозды ағза трансплантациясы: Ағымдағы жағдай мен мәселелерге шолу

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Түйіндіме

Ағзаларды трансплантациялау - соңғы жылдары қарқынды дамып келе жатқан Қазақстан медицинасының маңызды стратегиялық бағыттарының бірі. Бүкіл елдегі ғылыми мекемелер мен аймақтық клиникаларда әлемдік стандарттарға сәйкес келетін озық трансплантация технологияларын енгізуде айтарлықтай прогресс байқалуда. Алайда, бұл салада органдардың жетіспеушілігімен, аурудың дамыған кезеңдеріндегі адамдарға трансплантациялау қажеттілігімен, қайта трансплантациялау қажеттілігінің артуымен және иммуносупрессивті терапиямен байланысты жанама әсерлермен байланысты белгілі бір мәселелер туындауда.

Бұл шолуда біз Қазақстандағы паренхималық органдарды трансплантациялаудың ағымдағы жағдайын және елдегі трансплантацияға кедергі келтіретін проблемаларды қорытындыладық. 2023 жылдың желтоқсанына дейін Кохран кітапханасында, Medline және EMBASE-де әдебиеттерді іздеу жүргізілді. Іздеу қолмен және келесі түйінді сөздер бойынша жүзеге асырылды: Қазақстандағы трансплантация, бауыр трансплантациясы, бүйрек трансплантациясы, жүрек трансплантациясы, үйлестіру орталықтары, иммуносупрессия.

Трансланттауды үйлестіру және халықты донорлармен қамтамасыз ету қызметінің тиімді жұмысы үшін халық арасында ақпарат тарату бойынша ағартушылық науқандарды ұйымдастыруды, трансланттауды үйлестіру орталықтарының желісін кеңейтуді, келісім презумпциясы негізінде донорлық моделін құруды және адам органдарының еркін билік етуін жоюды қамтитын кешенді тәсіл қажет.

Түйін сөздер: *бауыр трансплантациясы, жүрек трансплантациясы, бүйрек трансплантациясы, орган донорлығы, Қазақстан.*

Трансплантация паренхиматозных органов в Казахстане: Обзор текущей ситуации и проблем

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Резюме

Трансплантация органов – одно из важных стратегических направлений медицины Казахстана, которое интенсивно развивается в последние годы. Заметный прогресс наблюдается во внедрении передовых трансплантационных технологий, соответствующих мировым стандартам, в научных учреждениях и региональных клиниках по всей стране. Однако в этой области существуют определенные проблемы, связанные с нехваткой органов, необходимостью трансплантации для лиц на поздних стадиях заболевания, растущей потребностью в повторной трансплантации и побочными эффектами, связанными с иммуносупрессивной терапией.

В этом обзоре мы стремимся обобщить текущую ситуацию с трансплантацией паренхиматозных органов в Казахстане и проблемы, препятствующие трансплантации в стране. Был проведен поиск литературы в Кокрановской библиотеке, Medline и EMBASE до декабря 2023 года. Поиск осуществлялся вручную и по ключевым словам: трансплантация в Казахстане, трансплантация печени, трансплантация почки, трансплантация сердца, координационные центры, иммуносупрессия.

Для эффективной работы службы координации трансплантации и обеспечения населения донорами необходим комплексный подход, включающий организацию просветительских кампаний по распространению информации среди населения, расширение сети координационных центров трансплантации, создание модели донорства на основе презумпцию согласия и устранение свободного распоряжения человеческими органами.

***Ключевые слова**: трансплантация печени, трансплантация сердца, трансплантация почки, донорство органов, Казахстан.*